PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

1 NAME OF THE MEDICINE

Leucovorin 50 mg/5 ml Fresenius Solution for injection or infusion

Leucovorin 100 mg/10 ml Fresenius Solution for injection or infusion

Leucovorin 200 mg/20 ml Fresenius Solution for injection or infusion

Leucovorin 350 mg/35 ml Fresenius Solution for injection or infusion

Leucovorin 500 mg/50 ml Fresenius Solution for injection or infusion

Leucovorin 1000 mg/100 ml Fresenius Solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 10 mg of folinic acid provided as calcium folinate.

Each 5, 10, 20, 35, 50, 100 ml vial contains 50, 100, 200, 350, 500 and 1 000 mg of folinic acid respectively (provided as calcium folinate).

Excipient with known effect:

3,14 mg/ml to 3,20 mg/ml (0,14 mmol/ml) sodium.

Sugar free.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion.

A clear, yellowish solution, free from visible particles.

pH: 6,5 - 8,5

Osmolality: 225 – 325 mOsmol/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

LEUCOVORIN FRESENIUS is indicated:

- to diminish the toxicity and counteract the action of folic acid antagonists such as methotrexate in cytotoxic therapy. This procedure is commonly known as calcium leucovorin rescue;
- for amelioration of the blood picture in a number of megaloblastic anaemias due to folate deficiency.

4.2 Posology and method of administration

Posology:

Megaloblastic anaemia secondary to folate deficiency

A dosage of 1 - 15 mg daily may be administered intramuscularly.

Calcium leucovorin rescue

Table 1:
LEUCOVORIN FRESENIUS rescue schedules following high-dose methotrexate

Methotrexate plasma levels	**Dose of LEUCOVORIN FRESENIUS**	**Duration of LEUCOVORIN FRESENIUS therapy**
< 5 µmol/l (24 hours after a 6 hour infusion)	10 -15 mg/m^2 every 6 hours	48 -72 hours
For every logarithmic concentration of methotrexate higher than 1 µmol, raise the dose of LEUCOVORIN FRESENIUS by a factor of 10 every 3 to 6 hours, until methotrexate levels fall below 0,01 µmol (at 24 – 30 hour post-infusion)		
< 1,5 µmol/l	10 – 15 mg/m^2 every 6 hours	48 hours
1,5 – 5 µmol/l	30 mg/m^2 every 8 hours	Until methotrexate level is <0,01 µmol/l
5 µmol/l	60 – 100 mg/m^2 every 6 hours	Until methotrexate level is <0,01 µmol/l

In general, up to 120 mg LEUCOVORIN FRESENIUS is given in divided doses, over 12-24 hours by intramuscular injection, bolus intravenous injection, or intravenous infusion, followed by 12 -15 mg intramuscularly, or 15 mg orally, every six hours for the next 48 hours. See “Method of administration below” and sections 6.2, 6.3 and 6.4.

In general, it is recommended that administration of LEUCOVORIN FRESENIUS be consecutive rather than simultaneous with methotrexate administration so as not to interfere with methotrexate’s antineoplastic effects. This is usually done within the first 36 - 42 hours of starting methotrexate infusion in a dosage that will produce blood levels equal to or greater than methotrexate blood levels. Duration of LEUCOVORIN FRESENIUS treatment also varies with the dosage of methotrexate and in patients with renal function impairment or pleural or peritoneal effusion.

Paediatric population

No data are available.

Method of administration

LEUCOVORIN FRESENIUS is administered parenterally as intramuscular injection or intravenous injection or infusion. Do not administer LEUCOVORIN FRESENIUS intrathecally (see section 4.4).

LEUCOVORIN FRESENIUS may be diluted with 5 % *m/v* glucose solution or 0,9 % *m/v* sodium chloride solution before use. For information on dilution for intravenous infusion see sections 6.3 and 6.6.

LEUCOVORIN FRESENIUS must not be mixed with other medicines except those mentioned above. See also section 6.2.

4.3 Contraindications

- Hypersensitivity to calcium folinate or to any of the excipients of LEUCOVORIN FRESENIUS (see section 6.1).

- LEUCOVORIN FRESENIUS should not be used as the only anti-anaemic medicine in the presence of pernicious anaemia or vitamin B12 deficiency. It must not be used in the treatment of pernicious anaemia or other megaloblastic anaemia secondary to lack of vitamin B12 since it may produce a haematologic remission while neurologic manifestations continue to progress.

4.4 Special warnings and precautions for use

LEUCOVORIN FRESENIUS should only be given as an intramuscular injection or intravenous injection or infusion. Do not administer LEUCOVORIN FRESENIUS intrathecally. When folinic acid has been administered intrathecally, following intrathecal overdose of methotrexate death has been reported.

General:

LEUCOVORIN FRESENIUS should only be used with methotrexate or 5-fluorouracil under the direct supervision of a medical practitioner experienced in the use of cancer chemotherapeutic medicines.

LEUCOVORIN FRESENIUS should not be given simultaneously with a folic acid antagonist to reduce or prevent clinical toxicity, as the therapeutic effect of the antagonist may be nullified.

LEUCOVORIN FRESENIUS treatment may mask pernicious anaemia and other anaemias resulting from vitamin B_{12} deficiency.

Many cytotoxic medicines – direct or indirect DNA synthesis inhibitors (hydroxycarbamide, cytarabine, mercaptopurine, thioguanine) – lead to macrocytosis. Such a macrocytosis should not be treated by folinic acid.

In epileptic patients treated with phenobarbital (phenobarbitone), phenytoin, primidone and succinimides there is a risk to increase the frequency of seizures due to decrease of plasma concentrations of anti-epileptic medicines (see section 4.5). Clinical monitoring,

possibly monitoring of the plasma concentrations and if necessary, dose adaptation of the anti-epileptic medicine during LEUCOVORIN FRESENIUS administration and after discontinuation is recommended (see also section 4.5).

5-fluorouracil and LEUCOVORIN FRESENIUS

LEUCOVORIN FRESENIUS may enhance the toxicity risk of 5-fluorouracil, particularly in elderly or debilitated patients. The most common manifestations are leucopenia, mucositis, stomatitis and/or diarrhoea, which may be dose limiting. When LEUCOVORIN FRESENIUS and 5-fluorouracil are used in combination, the 5-fluorouracil dosage has to be reduced more in cases of toxicity than when 5-fluorouracil is used alone.

Combined 5-fluorouracil/ LEUCOVORIN FRESENIUS treatment should neither be initiated nor maintained in patients with symptoms of gastrointestinal toxicity, regardless of the severity, until all of these symptoms have completely disappeared.

Because diarrhoea may be a sign of gastrointestinal toxicity, patients presenting with diarrhoea should be carefully monitored until the symptoms have disappeared completely, since a rapid clinical deterioration leading to death can occur. If diarrhoea and/or stomatitis occur, it is advisable to reduce the dose of 5-fluorouracil until symptoms have fully disappeared. Especially the elderly and patients with a low physical performance due to their illness are prone to these toxicities. Therefore, particular care should be taken when treating these patients.

In elderly patients and patients who have undergone preliminary radiotherapy, it is recommended to begin with a reduced dosage of 5-fluorouracil.

LEUCOVORIN FRESENIUS must not be mixed with 5-fluorouracil in the same IV injection or infusion (see section 6.2).

Calcium levels should be monitored in patients receiving combined 5-fluorouracil/LEUCOVORIN FRESENIUS treatment and calcium supplementation should be provided if calcium levels are low.

Methotrexate and LEUCOVORIN FRESENIUS

If methotrexate is administered intrathecally as local therapy and LEUCOVORIN FRESENIUS is administered concurrently, the presence of tetrahydrofolate may negate the antineoplastic effect of methotrexate.

Patients who experience delayed early methotrexate elimination are likely to develop reversible renal failure and all toxicities associated with methotrexate. For specific details on toxicity of methotrexate and reduction thereof, refer to the Professional Information of methotrexate.

The presence of pre-existing or methotrexate- induced renal insufficiency is potentially associated with delayed excretion of methotrexate and may increase the need for higher doses or more prolonged use of LEUCOVORIN FRESENIUS.

Excessive LEUCOVORIN FRESENIUS doses should be avoided since this might impair the antitumour activity of methotrexate, especially in central nervous system tumours where LEUCOVORIN FRESENIUS accumulates after repeated courses.

Resistance to methotrexate as a result of decreased membrane transport implies also resistance to folinic acid rescue as both medicines share the same transport system.

An accidental overdose with a folate antagonist, such as methotrexate, should be treated as a medical emergency. As the time interval between methotrexate administration and calcium folinate rescue increases, the effectiveness of LEUCOVORIN FRESENIUS to counteract the toxicity decreases.

The possibility that the patient is taking other medicines that interact with methotrexate (e.g. medicines which may interfere with methotrexate elimination or binding to serum albumin) should always be considered when laboratory abnormalities or clinical toxicities are observed.

The following should be monitored in patients where LEUCOVORIN FRESENIUS is used as a rescue in high-dose methotrexate therapy:

- Creatinine clearance should be performed prior to initiation of high-dose methotrexate therapy.
- Serum creatinine should be determined daily to detect developing renal dysfunction.
- Plasma methotrexate levels should be performed approximately 48 hours after methotrexate administration to determine the duration of LEUCOVORIN FRESENIUS treatment needed to maintain rescue. If levels are too high, repeat every 24 hours until normal (see section 4.2).

Seizures

LEUCOVORIN FRESENIUS may increase the frequency of seizures in susceptible children by counteracting the anticonvulsant effects of barbiturates, hydantoin anticonvulsants and primidone.

Sodium

LEUCOVORIN FRESENIUS solution for injection contains 3,14 mg/ml to 3,20 mg/ml (0,14 mmol/ml) sodium. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicines and other forms of interaction

When LEUCOVORIN FRESENIUS is given in conjunction with a folic acid antagonist (e.g. co-trimoxazole, pyrimethamine, methotrexate) the efficacy of the folic acid antagonist may either be reduced or completely neutralised (see section 4.5). Therefore it should not be given in conjunction with a folic acid antagonist.

LEUCOVORIN FRESENIUS should not be given within 2 hours of a dose of glucarpidase.

LEUCOVORIN FRESENIUS may reduce the effect of anti-epileptic medicines: phenobarbital, primidone, phenytoin and succinimides, and may increase the frequency of seizures (a decrease of plasma levels of enzymatic inductor anticonvulsant medicines

may be observed because the hepatic metabolism is increased as folates are one of the cofactors (see also sections 4.4 and 4.8)).

The efficacy and also the toxicity of 5-fluorouracil are enhanced by the concomitant administration of LEUCOVORIN FRESENIUS (see sections 4.2, 4.4 and 4.8).

Concurrent administration of chloramphenicol and LEUCOVORIN FRESENIUS in folate-deficient patients may result in antagonism of the haematopoietic response to folic acid.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

Refer to the package inserts of methotrexate, 5-fluorouracil and other medicines administered concomitantly for relevant information.

Fertility:

No data are available.

4.7 Effects on ability to drive and use machines

LEUCOVORIN FRESENIUS may increase the frequency of epileptic fits. Epileptic patients should be advised not to drive or handle machinery if this happens.

4.8 Undesirable effects

Tabulated summary of adverse reactions:

Immune system disorders *Less frequent:* hypersensitivity reactions, anaphylactic and anaphylactoid reactions Psychiatric disorders *Less frequent:* insomnia, agitation and depression after high doses Nervous system disorders *Less frequent:* increase in the frequency of attacks in epileptics (see also section 4.5)

Gastrointestinal disorders

Less frequent: gastrointestinal disorders, nausea, vomiting after high doses, enterocolitis, diarrhoea with higher grades of toxicity, and dehydration, resulting in hospital admission for treatment and even death

Skin and subcutaneous tissue disorders

Frequency unknown: pruritus, rash, hives

General disorders and administration site conditions

Less frequent: fever has been observed after intravenous administration.

Frequency unknown: injection site reactions, thrombocytosis

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

See section 4.8. Excessive amounts of calcium folinate may nullify the chemotherapeutic effect of folic acid antagonists.

Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Detoxifying agents for antineoplastic treatment; ATC code: V03AF03

Category A, class 8.3 Erythropoietics (haematinics)

Calcium folinate (leucovorin calcium) is the calcium salt of 5-formyl tetrahydrofolic acid. It is an active metabolite of folinic acid and an essential coenzyme for nucleic acid synthesis.

Calcium folinate is readily converted to other folic acid derivatives and replaces folic acid lost because of deficiency on administration of folic acid antagonists.

5.2 Pharmacokinetic properties

Absorption

Following intramuscular administration of the aqueous solution, systemic availability is comparable to an intravenous administration. However, lower peak serum levels (C_{max}) are achieved.

Metabolism

Calcium folinate is a racemate where the L-form (L-5-formyl-tetrahydrofolate, L-5-formyl-THF), is the active enantiomer.

The major metabolic product of folinic acid is 5-methyl-tetrahydrofolic acid (5-methyl-THF) which is predominantly produced in the liver and intestinal mucosa.

Distribution

The distribution volume of folinic acid is not known.

Peak serum levels of the parent substance (D/L-5-formyltetrahydrofolic acid, folinic acid) are reached 10 minutes after i.v. administration.

AUC for L-5-formyl-THF and 5-methylTHF were 28,4 ± 3,5 mg.min/l and 129 ± 112 mg.min/l after a dose of 25 mg. The inactive D-isomer is present in higher concentration than L-5-formyltetrahydrofolate. Folate is concentrated in the cerebrospinal fluid, although distribution occurs to all body tissues.

Elimination

The elimination half-life is 32 - 35 minutes for the active L-form and 352 - 485 minutes for the inactive D-form, respectively.

The total terminal half-life of the active metabolites is about 6 hours (after intravenous and intramuscular administration).

80-90 % is excreted with the urine (5- and 10-formyl-tetrahydrofolates inactive metabolites), 5-8 % with the faeces.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

Water for injection.

6.2 Incompatibilities

Incompatibilities have been reported between injectable forms of calcium folinate (including LEUCOVORIN FRESENIUS) and injectable forms of droperidol, 5-fluorouracil, foscarnet and methotrexate.

Droperidol

1. Droperidol 1,25 mg/0,5 ml with calcium folinate 5 mg/0,5 ml, immediate precipitation in direct admixture in syringe for 5 minutes at 25 °C followed by 8 minutes of centrifugation.

2. Droperidol 2,5 mg/0,5 ml with calcium folinate 10 mg/0,5 ml, immediate precipitation when the drugs were injected sequentially into a Y-site without flushing the Y-side arm between injections.

Fluorouracil

Calcium folinate must not be mixed in the same infusion as 5-fluorouracil because a precipitate may form. Fluorouracil 50 mg/ml with calcium folinate 20 mg/ml, with or without dextrose 5 % in water, has been shown to be incompatible when mixed in different amounts and stored at 4 °C, 23 °C, or 32 °C in polyvinyl chloride containers.

Foscarnet

Foscarnet 24 mg/ml with calcium folinate 20 mg/ml formation of a cloudy yellow solution reported.

6.3 Shelf life

18 months.

After first opening:

For single dose use only. Discard any unused solution immediately after initial use.

After dilution:

When diluted according to directions with 0,9 % sodium chloride solution or 5 % glucose solution, chemical and physical in-use stability has been demonstrated when protected from light.

Chemical and physical in-use stability after dilution to 1,5 mg/ml with either 0,9 % sodium chloride solution or 5 % glucose solution was demonstrated for up to 24 hours, at both room temperature (25 °C) and 2 °C – 8 °C, when protected from light.

Chemical and physical in-use stability after dilution to 0,2 mg/ml with 0,9 % sodium chloride solution was demonstrated for up to 24 hours at 2 °C – 8 °C, when protected from light.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the

user and would normally not be longer than 24 hours at 2 °C -8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (+2 °C to +8 °C)

Keep vial in the outer carton in order to protect from light.

For storage conditions of the diluted medicine, see section 6.3.

6.5 Nature and contents of container

The 5 ml, 10 ml, 20 ml, 35 ml, 50 ml or 100 ml vials are amber coloured, Ph. Eur Type I glass vial with grey chlorobutyl rubber stoppers and are respectively sealed with red, yellow, violet, white, brown and orange flip-off aluminium seals.

Pack sizes:

Packs of 1 vial, 5 vials and 10 vials for all fillings.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Prior to administration, LEUCOVORIN FRESENIUS should be inspected visually. The solution for injection or infusion should be a clear and yellowish solution. If cloudy in appearance or particles are observed, the solution should be discarded.

LEUCOVORIN FRESENIUS solution for injection or infusion is intended only for single use. Any unused portion of the solution should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

FRESENIUS KABI SOUTH AFRICA (PTY) LIMITED

Stand No. 7, Growthpoint Park

162 Tonetti Street

Halfway House

South Africa 1685

8 REGISTRATION NUMBERS

Leucovorin 50 mg/5 ml Fresenius: 50/8.3/0455

Leucovorin 100 mg/10 ml Fresenius: 50/8.3/0456

Leucovorin 200 mg/20 ml Fresenius: 50/8.3/0457

Leucovorin 350 mg/35 ml Fresenius: 50/8.3/0458

Leucovorin 500 mg/50 ml Fresenius: 50/8.3/0459

Leucovorin 1000 mg/100 ml Fresenius: 50/8.3/0460

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13 April 2021

10 DATE OF REVISION OF THE TEXT